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(54) **A direct tabletting auxiliary.**

(57) A direct tabletting auxiliary contains, in an intimate mixture, the essential components
A) from 60 to 98% by weight, based on the direct tabletting auxiliary, of microcrystalline cellulose, cornstarch, mannitol, lactose, sorbitol, cellulose powder, calcium sulfate, calciuöm phosphate, calcium carbonate, sodium starch glycolate or calcium carboxymethyl cellulose,
B) from 2 to 40% by weight, based on the direct tabletting auxiliary, of a binder selected from the group comprising hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, pregelatinized starch maltodextrin, polyvinylpyrrolidone, gelatin and α-, β- or γ-cyclodextrin, where the intimate mixture of A and B has been produced in the presence of water using a wet mixing process and simultaneous or subsequent drying.

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The present invention relates to a direct tabletting auxiliary based on a tablet filler, preferably microcrystalline cellulose (MCC) with a binder, preferably beta-cyclodextrin, the auxiliary having been prepared by a wet mixing process.

Currently used for direct tabletting, i.e. the dry mixing of tabletting auxiliary and active substance and compression, in the pharmaceutical industry are a number of carrier materials such as cellulose powder, dicalcium phosphate, sorbitol, MCC, dextrose, lactose or lactose/-cellulose.

The main requirements to be met by a direct tabletting auxiliary of this type are: good flowability, good compressibility under low pressure, and high loading capacity.

The tablets produced therewith should have satisfactory hardness, low friability and good disintegration and dissolution properties.

These requirements are only partly met by commercial products.

The method of direct tabletting is of particular interest to the pharmaceutical industry because, on the one hand, it allows stress-free processing of active substances and, on the other hand, the costs of processing and producing tablets are lower.

Microcrystalline cellulose has been used as auxiliary for direct tabletting for many years world-wide (eg. as Avicel® PH 101 and PH 102), and is described inter alia in USP XXII/NF XVII, page 1915, to which reference is made.

It is an object of the present invention to propose a direct tabletting auxiliary which meets the said requirements and, moreover, makes a higher loading capacity possible, which means that tablets with a content of active substance of from 70 to 75% can be produced, and addition of a disintegrant is unnecessary in most cases.

We have found that this object is achieved by a novel direct tabletting auxiliary containing, in an intimate mixture, the essential components

A) from 60 to 98% by weight, preferably from 80 to 98% by weight, based on the direct tabletting auxiliary, of a tablet filler selected from the group comprising microcrystalline cellulose, cornstarch, mannitol, lactose, sorbitol, cellulose powder, calcium sulfate, calcium phosphate, calcium carbonate, sodium starch glycolate or calcium carboxymethyl cellulose, preferably microcrystalline cellulose and

B) from 2 to 40% by weight, preferably from 2 to 20% by weight, based on the direct tabletting auxiliary, of a binder selected from the group comprising hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, pregelatinized starch maltodextrin, polyvinylpyrrolidone, gelatin and α-, β- or γ-cyclodextrin, preferably β-cyclodextrin where the intimate mixture of A and B has been produced in the presence of water using a wet mixing process, in particular wet granulation process, spray granulation process or spray drying and simultaneous or subsequent drying.

Suitable binders B) are hydroxypropylmethylcellulose as commercially available under the name PHARMACOAT®, type A, USP XXI, from Shinetsu, Japan, or METHOCEL®, type B, from Dow Chemical, hydroxypropylcellulose, eg. KLUCEL® from Hercules, USA, gelatin NF XVI, and polyvinylpyrrolidone of K value from 20 to 95, preferably 28 to 32. The latter is described, for example, in R. Vieweg, M. Reiher and H. Scheuerlen, Kunststoff-Handbuch, 1971, volume 11, page 558, Carl Hanser-Verlag, Munich, or Ullmann, 4th edition, volume 19, pp. 385-386. For the definition of the K value, see the povidone monograph USP XXI, 1985, to which reference is made.

However, the preferred binders are α-, β- and γ-cyclodextrins, preferably β-cyclodextrin, as marketed under the name KLEPTOSE® by Roquette.

By wet mixing processes are meant all processes with which the components A and B which have been moistened with water or an alcohol/water mixture, ie. usually with a quantity of water which is insufficient to dissolve the binder completely, are uniformly mixed in a mixing apparatus and simultaneously or subsequently dried.

The procedure for spray granulation is, for example, such that a mixture of MCC and the binder is introduced into the fluidized bed and, with the temperature slightly elevated, eg. at from 40 to 60°C, sprayed with water, resulting in a dried product.

Wet granulation entails, for example, mixing MCC with the binder in a suitable mixer, pouring water in while continuing to stir, and drying the moist material after it has been passed through a screen, or moistening the tablet filler with a solution or suspension of the binder in water. The moist material is then screened and dried.

The spray drying is usually carried out in such way that an aqueous suspension of the tablet filler A and component B is sprayed in a suitable spraying apparatus concurrently or countercurrently with the drying air at elevated temperatures, eg. at an inlet temperature of the drying air or up to 120°C.

The said processes are expediently used, starting from finely powdered MCC, to prepare a powder with a narrow particle size distribution of, for example, from about 25 to 250 μ with from 60 to 70% in the range

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from 40 to 75 µ. Of the methods which have been mentioned, wet granulation is preferred and gives particularly good results.

The mixtures according to the invention which are obtained have excellent tabletting properties and are distinguished from known direct tabletting auxiliaries by, in particular, good flowability, good compressibility under low pressure and excellent disintegration properties with high hardness and low friability of the tablets.

The examples which follow describe both the preparation of the mixtures according to the invention and the production of tablets, comparing with direct tabletting auxiliaries which have been prepared by physical mixing.

Examples

I	MCC wet (51% solid content) β-Cyclodextrin Distilled water	5.0 kg 670 g 2.9 kg

← 38% H_2O

Suspend 380 g β-Cyclodextrin in 2.9 kg water and add the suspension to the wet MCC in a kneader. After 5 minutes intensive blending pass through a sieve (0.5 mm) and dry the material at 80 ° C. After drying pass it again through a sieve (0.250 mm) (water content below 6%).

II	MCC wet (51% solid content) β-Cyclodextrin Ethanol 95%	5.0 kg 210 g 2.0 l

Suspend 190 g β-Cyclodextrin in 2.0 l Ethanol 95%, mix intensively in a blender with 5 kg of wet MCC, pass through a sieve (0.5 mm) and dry the material at 80 ° C. Pass again through a sieve of 0.250 mm.

III	MCC β-Cyclodextrin Water	5.0 kg 1.25 kg 4.5 kg

← 41,9%

The stirred suspension of β-Cyclodextrin in water is sprayed continuously in fluidized bed granulator on MCC. The inlet air temperature was about 60 ° C.

The drying process is finished, when the water content is below 6% in the final product. The material is then sieved through 250 micron screen.

The mixtures of the following compositions were prepared by the same methods.

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1.	MCC β-Cyclodextrin	90 parts 10 parts
2.	MCC β-Cyclodextrin	85 parts 15 parts
3.	MCC β-Cyclodextrin	70 parts 30 parts
4.	MCC β-Cyclodextrin	60 parts 40 parts
5.	MCC β-Cyclodextrin	75 parts 25 parts
6.	MCC PVP-K 30	92.5 parts 7.5 parts
7.	MCC α-Cyclodextrin	80 parts 20 parts
8.	MCC γ-Cyclodextrin	80 parts 20 parts
9.	Corn starch Cyclodextrin	80 parts 20 parts
10.	Mannitol β-Cyclodextrin	70 parts 30 parts
11.	Sodium starch-glycolate Beta-Cyclodextrin	80 parts 20 parts
12.	Calcium carboxy methylcellulose Beta-Cyclodextrin	80 parts 20 parts
13.	Calcium phosphate Beta-Cyclodextrin	80 parts 20 parts

The resulting products have the following properties:

Angle of repose:	38 - 55 ° C
Bulk density:	278 - 470 g/l
Particle size: distribution:	> 75 micron max. 75% > 250 micron max. 1%.

Tabletting examples:

A)

Mixture of Ex. I	99.5 parts
Lubricant magnesium stearate	0.5 part

The components are mixed for 5 minutes and then converted in a rotary tabletting machine into biplanar tablets of diameter 12 mm, weighing 500 mg, with a moderate pressure (5-10 kN). The resulting tablets have a hardness of 180-290 N and a disintegration time of 5 min.

Compared to that a physical mixture of the said powdered components proves to be distinctly less

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satisfactory than the novel tabletting auxiliary.

The loading capacity is important for direct tabletting auxiliaries. The substances preferably used for testing the loading are those which are known to be difficult to tablet such as paracetamol or acetylsalicyclic acid. Besides high loading, also important are good disintegration properties, hardness and friability.

B) The tabletting is carried out as described under A) using

Paracetamol	350 parts
Mixture of Ex. I	148 parts
Stearic acid powder	2 parts

The loading is thus 70%, but loading up to 80% is possible.

Weight:	500 mg
Hardness:	115 N
Disintegration:	1 - 2 min
Friability:	0.5%

Coparison with direct tabletting using Avicel® pH 101 (MCC from FMC) yields the following results:

Weigth:	500 mg
Hardness:	95 N
Disintegration:	5 min
Friability:	0.3%

Thus a lower pressure is required on use of the novel direct tabletting auxiliaries to obtain the same tablet hardness.

C) The procedure is as in Example A), using

Acetylsalicylic acid	400 parts
Mixture of Ex. I	60 parts
Potato starch	35 parts
Stearic acid powder	5 parts

Corresponding to a loading of 80%

Weight:	500 mg
Hardness	97 N
Disintegration:	5 min
Friability:	0.2%
Diameter:	12 mm

Comparison of the direct tabletting with MCC in place of mixture 5 yields the following results:

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Weight:	500 mg
Hardness:	72 N
Disintegration	5-10 min
Friability:	0.3%
Diameter:	12 mm

Claims

1. A direct tabletting auxiliary containing, in an intimate mixture, the essential components
   A) from 60 to 98% by weight, based on the direct tabletting auxiliary, of a tablet filler selected from the group comprising microcrystalline cellulose, cornstarch, mannitol, lactose, sorbitol, cellulose powder, calcium sulfate, calcium phosphate, calcium carbonate, sodium starch glycolate or calcium carboxymethyl cellulose,
   B) from 2 to 40% by weight, based on the direct tabletting auxiliary, of a binder selected from the group comprising hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, pregelatinized starch maltodextrin, polyvinylpyrrolidone, gelatin and α-, β- or γ-cyclodextrin, where the intimate mixture of A and B has been produced in the presence of water using a wet mixing process and simultaneous or subsequent drying.

2. A direct tabletting auxiliary as claimed in claim 1, wherein the content of
   A) is from 80 to 98% by weight and of
   B) is from 2 to 20% by weight.

3. A direct tabletting auxiliary as claimed in claim 1, wherein the binder is β-cyclodextrin.

4. A direct tabletting auxiliary as claimed in claim 1, which is prepared by wet granulation.

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EUROPEAN SEARCH REPORT

Application Number

EP 90 12 2804

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	EP-A-0 192 173 (BASF AG) * Page 1, lines 3-11; page 1, line 37 - page 2, line 35; page 3, lines 23-26,32-36; pages 4-6; examples 1-12; claim 1 *	1,2,4	A 61 K 9/20
Y		3	
Y	CHEM. PHARM. BULL., vol. 32, no. 2, 1984, pages 665-669; E. FENYVESI et al.: "Properties of Cyclodextrin Polymers as a tabletting aid" * The whole document *	3	
X	EP-A-0 265 951 (STAUFFER CHEMICAL CO.) * Page 2, lines 1-2; page 4, lines 5-23; pages 11-13, examples 10-18; claims 5,8-10 *	1,2,4	
Y		3	
Y	EP-A-0 140 203 (MERCK PATENT GmbH) * Page 2, line 11 - page 4, line 9; page 6, example 3; claims *	3	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	09-07-1991	BOULOIS D.J-M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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